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EDITORIAL

BIOCHEMISTRY AND ANIMAL HEALTH

THE Animal Health Trust (formerly the Veterinary Educational Trust) had the good fortune to arrange that the Fison Lectures for 1948 were delivered by Professor L. Seekles, of the University of Utrecht. Three lectures, under the title of "The Biochemical Approach to Animal Disease" were delivered: the first is reproduced in this issue of THE VETERINARY JOURNAL, and the others will appear in later numbers.

Biochemistry and its relationship to animal health and disease is, comparatively speaking, a recent subject. The older members of the Veterinary Profession had little, if any, association with it in their training days: now, of course, it is an important subject in pre-clinical teaching in veterinary schools. Students now are receiving explanations for some of the conditions of health and disease which were but vaguely understood but a few years ago. Whole departments in schools and research institutions are given up to the study and teaching of this complex subject, so that we now can see much more clearly the different processes involved in health and how their upsetting, sometimes in only a small degree, causes a deviation from the normal, i.e., disease. The subject embraces a large number of sections of science, and it is interesting to observe, year by year, how biochemical explanations can be found for some of the hitherto unexplained causes of ill-health in livestock. We owe much to the early pioneers in the subject who applied biochemistry and biochemical methods to the study of disease. As more and more trained biochemists apply their knowledge to veterinary medicine, so does our understanding become more advanced. Biochemistry is bound up with physiological processes: in many instances the one has a bearing on the other and the two sciences, as applied to a problem, have to be studied side by side.

Many examples of the value of biochemistry in our understanding of health and disease could be given: much of the outstanding work is dealt with in the Fison Lectures. Trace or minor element influence on health will serve as one example. While much has been known of the major elements for a long time, our appreciation of the part played by minor elements in the maintenance of

health is recent. Who would have predicted many years ago that cobalt, for example, in such minute amounts, was essential to good health and development? Now, of course, it is a recognised procedure to consider trace element deficiency in studying the cause of disease. The relationships of the soil, the pasture and animal health are gradually being understood, and much of the credit for this understanding belongs to the biochemists. Not only do their studies tell us the cause of some of these vague conditions; they also point the way to their prevention and cure. Excess of some trace elements has also been shown to cause ill-health, and here again the biochemist comes to our aid in finding for us means of balancing the various elements concerned. The study of endocrine functions and the parts played by hormones in maintaining health and normal functions falls partly into the sphere of the biochemist. We look to them also for new knowledge on that imperfectly understood group of diseases classified as metabolic disturbances. Although biochemistry has assisted us greatly, we have still to look to biochemists for further explanations and help. The subject is growing and it is gratifying to see that each year more young veterinarians are undergoing post-graduate training which will enable them to carry out research work on some group or groups of subjects in biochemistry. With a veterinary background, followed by a training in biochemistry, we should have the type of person who can appreciate the problems facing us and who, following their study and with the collaboration of others, devise means which can be applied in the field.

GENERAL ARTICLES

THE BIOCHEMICAL APPROACH TO ANIMAL DISEASE

The Fison Lectures, 1948, of the Animal Health Trust

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Utrecht University

I—The Biochemical Basis of Veterinary Science
General Lecture

AMONG the fundamental sciences applied to research in veterinary problems, biochemistry has proved to be of primary importance. Biochemistry enables us to get an insight into the material changes of the animal body.

Life is inseparable from biochemical reactions. These reactions occur in all tissues and organs. Biochemical processes dominate respiration, feeding, metabolism, growth, the functioning of the muscles, the conduction of stimuli—in short, all life's functions in health and disease. A thorough knowledge of what chemically occurs in the body is of supreme importance for our scientific insight into veterinary problems. The practical results of a purposeful study of biochemistry can scarcely be overrated. Biochemistry is a powerful tool to use in tracing the causes, the diagnosis and the control of diseases, and in helping increase of production.

In fact, biochemistry has during the last 25 years been so applied. I need only remind you of the work done in South Africa in the control of aphosphorosis, a disease caused by a shortage of phosphorus in cattle food. And, further, of the work done in this country, the Dominions and the United States of America concerning the importance of minor elements for livestock. The work done in the Netherlands in the control of metabolic diseases of cattle, horses, sheep, pigs and poultry deserves to be mentioned. It would be impossible to give the names of the numerous scientists who have taken their share in these investigations.

Biochemical Disorders Caused by Domestication

It is an undeniable fact that biochemical disorders often occur in our production animals: cattle, sheep, poultry and, to a lesser degree, horses. In these disorders a change of the chemical composition of blood and body tissues is observed. In many cases, morphological changes do not occur. Sometimes these metabolic disorders show themselves in animals kept within a more or less limited area—for instance, on certain kinds of soil. Of course, one should in these cases begin by looking for local causes. It stands to reason that it is of the greatest importance that there should be a good co-operation between biochemists and veterinary surgeons practising in these areas, for the latter have the best opportunities of observing these disorders and of reporting them. Occasionally a disorder is not confined to limited areas, but is of a more general character. In this instance, one should consider causes of a more general kind, and here one is less dependent on local observation.

But it is not only veterinarians who should be highly interested in these problems. It is important to emphasise that farmers may essentially assist by accurate observation of the animals and by reporting abnormal behaviour to the veterinary practitioners. The sooner and the more completely this is done, the more efficient will be therapy and prophylaxis. Close co-operation between farmers and veterinarians is an indispensable condition to a successful fight against disease in livestock.

It is not difficult to give some causes which promote the frequent occurrence of metabolic disturbances in production animals. The domestication of our livestock and the enormous speeding-up of the rate of growth and production are often accompanied by a way of living which is, in many respects, irrational for the animal.

Even more than civilized man, our production animals have in a certain sense become physiological artifacts. It goes without saying that the natural resistance will become impaired and functional disturbances will occur.

Disorders in Relation to Nutrition

Nutrition, which is sometimes unsuitable, often plays an important part in the origin of undesirable conditions in cattle. In preparing the food, with an eye to what may be considered necessary with respect to production and rate of growth, the needs of the body are sometimes not sufficiently considered. The nature of the food of our production animals is, in a great measure, determined by the price of vegetable foodstuffs in the world market. In the years when American corn was cheap this foodstuff was used in almost unlimited quantities in fattening pigs, in spite of its unfavourable mineral composition. The bad results did not fail to make their appearance. For the biochemist who studies the influence of nutrition on the animal body, an almost unlimited field of activity lies fallow, even to-day.

In the majority of cases, nutritional disorders proceed side by side with a complex of biochemical and clinical symptoms. The investigations carried out in the Utrecht Laboratory for Veterinary Biochemistry showed that these symptoms in some respects bear a similarity to, but also some differences from, the biochemical and clinical symptoms found in the case of disorders of quite different origin. I may group the causes of these disturbances together and designate them by the word "autointoxication." *It is important to notice that features of autointoxication may arise in cases in which the composition of the food is quite normal.* After all, the development of symptoms, if any, of autointoxication is determined by the way the animal reacts to the food administered. The reaction of one animal to the administration of a normal food may be quite different from the reaction of other animals on the same farm.

An accurate determination and study of biochemical symptoms is not only scientifically but also practically of importance. By this means we are often able to recognise the disorders at an early stage and show the way to a rational control of the evil.

Biochemistry in Veterinary Research and Veterinary Education

The biochemical method of investigating veterinary problems gives us two ways of approach. In the first, one can take a purely practical standpoint. This

means that a problem is solved in proportion to practical requirement. The chief aim is, then, to find a therapy and prophylaxis for the disorder. When these have been found they are applied with more or less success without troubling further about the deeper causes of the disease and the method of its cure. In the second manner of approach, one may take the view that it is not sufficient to develop a therapy, but that it is also necessary to investigate as completely as possible the nature and causes of the disease and its cure. This involves the necessity of investigating the biochemical characteristics of the normal animal. This way of proceeding has been followed in the Netherlands since 1925, when the Veterinary College at Utrecht was added as a sixth Faculty to the State University. This involved the establishment of a Chair for Veterinary Biochemistry, when it became possible to study the veterinary-biochemical problems in a scientific way in a laboratory specially adapted for this purpose, and to teach these problems to veterinary students. A very efficient co-operation between the veterinary clinics of the Faculty and the veterinary practitioners in the country, who are showing a keen interest in the work of the laboratory and are constantly kept posted both orally and in the literature, guarantees a synthesis between pure and applied science.

This latter method has some advantages. Owing to a better insight into the nature of a disorder, therapy and prophylaxis are placed on a firmer footing. The thorough knowledge of the biochemical properties of the sound, healthy organism makes the study of the disorders in the same animal species much easier. At the same time, it prevents the danger of pushing specialisation too far. At the beginning this way of working gives more trouble to the scientist, but in the end scientific work will proceed more rapidly. The same is true for the establishing of practical results.

Biochemical Features of Disease

I now draw your attention to a further consideration of the biochemical features of disease which may occur in functional disturbances. They have been shown to be of great importance in the study of scientific and practical problems. I will illustrate this with a simple example.

The quantity of calcium daily leaving the body of a milk cow in full lactation often amounts to about twelve times the quantity of calcium present in the blood of the same animal. Because the calcium of the milk is obtained from the blood, it follows that the calcium in the blood must be replaced about twelve times every day. Generally speaking, it may be said that in the body of a milk cow, which is in physiological balance, there is, for several months at a stretch, a daily transference of calcium from the point of entry into the body of the cow—viz., the intestine—via the blood, to the mammary gland. (The absorption of calcium from the bones is not considered.) So long as the cow is in a healthy state, the calcium value of the blood is always at about the same average level. This is necessary to enable the various organs to work normally. In this condition, the absorption of calcium from the food, its passing into the milk, and the calcium value of the blood must be perfectly balanced.

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If, however, under the influence of certain factors, the normally existing regulation of calcium metabolism is disturbed for instance, when the supply of calcium to the blood becomes less than its transference to the mammary gland (and other body tissues)—the result will be a decrease of the calcium value of the blood. This decrease is one of the most serious biochemical symptoms of milk fever. It may be accompanied by functional disturbances in various organs, evidenced as clinical symptoms of disease.

What I have said about the calcium may also hold good in principle for other inorganic and organic substances of the blood and the tissues in general. Under such conditions, the biochemical composition of the body tissues may differ greatly from the normal state.

If we consider the abnormal state to which our production animals have been brought by man's interference, we should be surprised that, under the conditions I have sketched, their body functions remain normal in the majority of them. It is not at all surprising that we find functional disorders in many of these animals.

Biochemical Regulations

The normal state in the human and animal body is characterised by a high degree of constancy in the chemical composition of blood and other body tissues. In functional disturbances this constancy may no longer hold good with resulting variation in the chemical composition of blood and other tissues. In studying these problems the first question the biochemist asks himself is, how is the balance of functions, leading to the stationary condition, the so-called "biochemical balance" in the organism, brought about? The next is, which factors contribute to the disturbance of this balance with the occurrence of clinical and biochemical symptoms of disease?

In answering these questions we use a general line of thought which is a good guide in research. It consists of simple, universally accepted facts, and the results of many years of experimental observation.

When we consider the different kinds of symptoms in the disorders which have been observed, we may point to the correlation of the numerous changes which evidently take place in the animal body, changes about whose complicated mechanism we are in many cases still in the dark. In this regulating system the autonomic nervous system, the endocrine glands and their products—the hormones —the reticulo-endothelial system, and the corpuscular components, e.g., of the blood, are all involved. The electrolytes rank foremost in the regulating system, but substances like the blood sugar, urea, vitamins (aid other bio-catalysers) also play an important part.

I shall give some examples to illustrate this point. Changes of the "*tonus*"—that is, changes in the state of sensitiveness of the autonomic nervous system—result in changes in the functioning of the endocrine glands. The reverse is also true. The concentrations of the electrolytes in the tissues are further bound up with the activity of the autonomic nervous system and the endocrine glands. The "membranes" (interfaces) and the physico-chemical processes ensure that the

mutual concentration-differences remain. For this, among other things, an activity of the cell is required. Whenever this activity is abnormal, due to certain influences, the constellation of ions in the cell—and potentially in the surrounding body fluids—will undergo a change. Thus, in disorders like milk fever and grass tetany an abnormal partition of minerals—mainly calcium, magnesium and phosphates—between blood and tissues has been shown to exist. This leads *inter alia* to a decrease of calcium ion activity in the blood which is not due to any deficiency of calcium in the diet or to any loss of calcium by the way of the mammary gland. It might be expected that the mineral changes in the blood, *cæteris paribus,* would cause reciprocal changes in tissues and other body fluids. Though the extent of these changes could not be determined exactly, in cases of malnutrition we were able to show a correlation between an increase of calcium ion activity in milk and a decrease of the calcium level of the blood, pointing to a lowering of calcium ion activity in this body fluid.

By an intricate play of correlative—that is to say, synergistic and antagonistic —actions, a state of sufficient stability and sensitiveness is preserved in the animal body. In principle, this normal state can also be biochemically determined, with the help of values, spread on both sides of so-called " normal concentrations " and concentration-proportions.

When we follow this line of thought it will be clear that dysfunctions of different kinds may lead to abnormal biochemical proportions in the cells and the body fluids. In correlation with this also other variable functions, such as metabolism, temperature of the body, blood pressure, blood distribution and the percentage of several forms of blood cells, may be altered.

If the extent of dysfunction of one or more organs, arising from the intensity of certain stimuli of an internal or external nature, exceeds the normal limits, unstable conditions in the organism of the animal and even disturbances of the biochemical balance may be the result. They may be attended by more or less characteristic features of " disease " of very different kinds. The etiological factors which have stimulated the occurrence of the disorder may in fact differ as to the point and the intensity of the attack.

One of the most characteristic phenomena, which one can often observe when a state of altered " balance " recovers, is the symptom of over-compensation, i.e., a going beyond the state of balance. This is sometimes attended by features of " disease " of a nature other than the original. It may occur from sudden, quick and strongly acting stimuli, for instance, acute infections (intoxications), administering of hormone-preparations, vitamins, electrolytes, etc., in general factors which are able to influence the regulating system. Thus when rickets is rapidly cured by administration of large quantities of vitamin D, phosphorus features of tetany may arise. However, if the influence exercised by the stimuli mentioned does not go beyond certain limits, the organism may permanently or temporarily be restored to its normal or apparently normal state.

Because, as I have already explained, the different factors influence one another in a correlative way, it is easy to understand that one stimulus is able to bring several variables back to the state of " balance " at the same time. It will

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also be clear that a similar improvement of the condition may be brought about by more than one means. In many cases it is indeed extremely difficulty, if not impossible, to judge the "specificity" of a means, or to determine whether a certain result should be called primary or secondary.

It may be useful to point out that when in a line of thought like this I speak of functional changes, I do not mean to suggest that in all cases these changes should be considered to be the opposite of changes of a morphological nature. I cannot point out too emphatically that a great many biochemical reactions which take place in the animal body are inseparable from the function of the living cell. This means that the direction and velocity of the biochemical reactions are dependent to a great extent on the structure of the living tissue. One should consider this coherence of cell-structure and function as one dynamic entity. However, in many cases of functional disturbance the changes of structure will be of a colloid-chemical nature and not detectable by the methods usually applied in histology. A schematic representation of the regulating system, which is far from being complete, is given below.

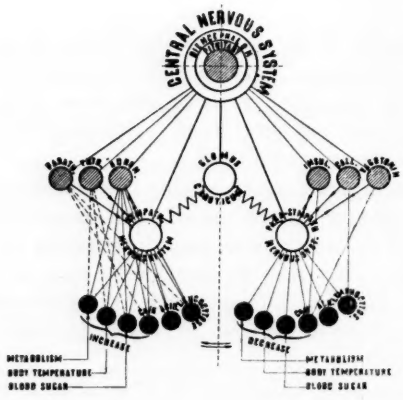

FIG. 1

Scheme of the regulating system in the animal body.

The scheme in Fig. 1, which illustrates the relationship of the biochemical constellation in the tissues with the physiological function of the organs, will become more useful as a guide to experimental research as the quantitative character of mutual relations comes more to the fore.

A Biological Basis for the Prevention and Cure of the Functional Disturbances of Milk Fever

A well-known disturbance of "balance" occurs in milk fever in cattle and apparently also in typical cases of acetonemia in cattle and sheep.

The results of recent experiments, which were carried out in my laboratory, make it highly probable that the forced development of the cow as a milk-producer causes a hyperfunction of the pituitary gland. This gland shows a size-increase of as much as twice its original weight during pregnancy. The result is a flooding of the organism with hormones, produced by this organ at the time of parturition and shortly afterwards. Owing to a correlative influence of internal secretions of other organs a complete dysfunction of hormonal regulation develops. A single stronger stimulus—parturition in the case of milk fever—makes it possible for the latent state to pass into a condition with a manifest complex of symptoms. With respect to this hypothesis of "hormonal intoxica-

tion," there is, in a certain sense, a confirmation in the biochemical and clinical symptoms observed, because the features of " disease " develop for the greater part as was expected.

Preventive measures concerning milk fever should be directed against the development of the pituitary gland during pregnancy. Although the experimental work has not been completed, evidence has been obtained that treatment by means of traces of iodine previous to parturition may be effective.

It is also clear that the restoring of the normal state in the organism, i.e., *a cure,* may be brought about in various ways (Fig. 1). If only an adequate stimulus is applied it does not, in principle, matter so much in which exact place of the regulation system one interferes, because the various components of this system are all correlatively connected.

In milk fever the activity of the para-sympathetic nervous system is showing a relative increase. Balance may be restored by stimulating the sympathetic system. This may be done in various ways, e.g., by administering calcium, or by exercising mechanical pressure in the mammary gland, i.e., by insufflation of air. It is also possible to effect a cure by injecting a hormone from the adrenals, or from the parathyroid gland. These methods are in fact not the only ones. It goes without saying that in practice the quantitative side of this problem ought to be considered, because one stimulus works more quickly and effectively than another. But this circumstance does not affect the fundamental utility of the different methods.

Instability of Milk due to an Increased Activity of Calcium Ions

A second example of a biochemical disturbance is a particular form of instability of milk.

In the late 20s and the early 30s of this century much trouble was experienced in the Netherlands from the frequent occurrence of curdling of fresh milk on boiling and even during transportation or storing for a short time. This condition was called " het Utrechtse melkgebrek " (the *Utrecht abnormality of milk*). It appeared at first in the Dutch province of Utrecht and gradually was found in the other provinces of the Netherlands: now it has spread all over the country, though the frequency of its occurrence seems to have considerably decreased as compared with its first appearance in the low countries.

Milk showing the typical " Utrecht-abnormality " proved to be quite normal in respect of " total " chemical composition, acidity determined by titration and pH. Bacterial count was shown to be normal, so the common diseases of the mammary gland could be excluded as possible causes. The animals were in good health and the blood showed normal calcium value.

In addition to the typical " Utrecht-abnormality of milk," which may probably be related to a luxurious diet, a non-typical form due to malnutrition was shown to occur in the Netherlands. It occurs in cattle as well as goats kept on heath or on pasture of bad quality, e.g., from moorland and poorly manured soils. The condition has been observed once in sheeps' milk. The non-typical abnormality often disappears on removing the animals to a better pasture.

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The non-typical condition of decreased stability may also occur in winter, when the animals are kept on too poor a diet, e.g., on bad hay and straw or on silages of grass and beetroots stored for more than a year. We observed several cases of this kind in cattle displaced from the battle regions during the last war. The condition was shown to be very persistent. Among these cases we sometimes observed a low total calcium content and other changes in the chemical constitution of milk, indicating a state of severe starvation. Blood serum sometimes showed a mineral disturbance, i.e., a decreased calcium content.

A more exact investigation revealed the remarkable fact that both in the typical and the non-typical form the decreased stability depends mainly upon a disturbance of the normally-existing mineral balance in milk. Although in the typical form the total calcium value of the milk was found to be normal, this mineral was shown to be present to a higher extent in an active form, so-called calcium ions, which causes curdling of the casein of the milk.

In both forms stabilisation of the abnormal milk may be effected by adding substances to the milk which combine with calcium ions to form inactive calcium complexes (Fig. 2).

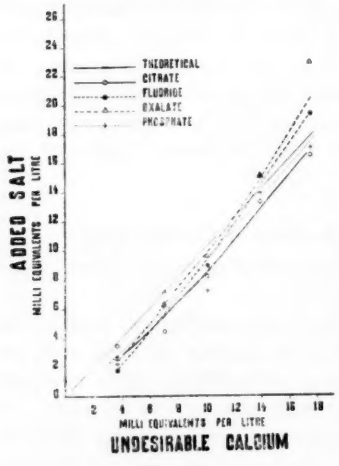

FIG. 2

Stabilisation of milk by added salts, at normal pH.

It is important to observe that among the drugs mentioned in Fig. 2 only sodium citrate is suitable for stabilising milk.

Sodium citrate is a normal constituent of milk. The quantity required for stabilisation depends on the extent of the instability. As a rule the quantity of sodium citrate required for stabilisation is shown to be rather small, so that milk treated in this way will not exceed the normal limits of variation with respect to chemical constitution, including pH. It shows very little difference from normal milk and may be sterilised or evaporated for manufacturing purposes and boiled for consumption or other domestic purposes.

The typical kind of "milk-abnormality" was often successfully corrected by treating cattle with sodium citrate. The drug may be administered by mouth in daily quantities of 50 grams for several days. It may equally well be administered subcutaneously in a 10 per cent. sterile solution, containing 30 grams of the crystallised salt. If necessary this treatment has to be repeated on several subsequent days.

Correction of the abnormality in non-typical cases by means of sodium citrate was shown to be hardly possible. Especially were cases of severe starvation found to be very resistant. In less advanced cases of malnutrition, removing to better pasture or the administration of a diet of better quality will sometimes suffice.

It is important to know something about the cause of the abnormality.

As mentioned above, we observed the typical form of "Utrecht-abnormality

of milk" in cows in perfect health. Its occurrence was shown to be independent of the kind of soil: heavy river clay, peat bog, sandy soil or mixtures. Sometimes it occurred early in the spring, while the cattle were still in the byre, and it lasted throughout the summer—while they were on pasture—until the autumn. In other cases the animals recovered spontaneously after several days. However, they often showed a relapse. From a single farm all the milk cows or only a few might show the abnormality.

As a rule, in the years in which the condition occurred most frequently, a good deal of concentrates was being fed. Diet was not always suitable in those days. However, deficiencies hardly occurred, the diet being rather luxurious. A definite relation between the occurrence of "milk-abnormality" and the diet could not be established. Attention should be drawn, however, to the coincidence of a high frequency of "luxury diseases" in cattle and the frequent occurrence of the "Utrecht-abnormality" of milk. This coincidence was observed about the 30th year of this century, in a period of economic plenty. It is well known that unsuitable feeding in heavy milking cows and other factors of management, including the heavy fertilising of pasture, may be considered to be more or less remote causes of metabolic disorders in cattle. Disorders in health may be accompanied by disturbances of the chemical balance. As was already pointed out, in recent years a theory has been developed according to which those conditions were related to "auto-intoxications" arising from different origins. In this way the causes of the appearance of disorders of rather complex nature, in which the sympathetic nervous system regulation is involved, may become more or less clear.

One of the more simple kinds of unsuitable feeding is the administration of large quantities of mineral substances, e.g., calcium salts. This was often practised in the period about the year 1930, in the prophylaxis of disorders like milk fever and grass tetany or to supplement the intravenous calcium therapy in the prevention of a relapse. For prophylactic purposes rather large and sometimes excessive quantities of minerals—mainly calcium carbonate—were fed for several months before and after parturition. (Since then a more scientific basis concerning the addition of mineral substances to the diet has been introduced.) In the prevention of relapse of milk fever and similar disturbances the daily administration of quantities of calcium chloride up to 80 grams for a period of several days to one week was not exceptional. Whether there exists a correlation between the high frequency of "milk-abnormality" and the administration of excessive quantities of calcium salts is not quite certain. It is thought to be rather improbable that the feeding of calcium salts would have been the principal cause of the "Utrecht-abnormality of milk." However, this factor should not be neglected. Experiments carried out in the United States of America are showing that daily feeding of 50-200 grams of calcium carbonate may provoke instability of milk. (The total calcium content of milk was shown not to be altered in these cases, just as in cases of typical abnormality of milk.)

Grass Tetany (lactation tetany) and similar Forms of Gastro-intestinal Autointoxication

In a third disturbance of the balance in cattle, grass tetany (lactation tetany),

which occurs mostly at the beginning of the grazing season and apart from parturition, we have another example of the influences of domestication. The features of "disease" should be attributed here, however, to other causes, connected with the sudden change of the animal from the byre to the pasture. Without any doubt the abnormal diet of large quantities of young grass of abnormal composition takes a prominent place among the stimuli which act in this condition. In many cases serious disturbances in the functioning of the intestinal tract occur, which may lead to autointoxication, originating in the intestine. There is every probability that in this autointoxication of the organism, in the majority of cases one must look for one of the most important causes for the development of the biochemical and clinical symptoms connected with them. Probably the poisons originating from abnormal fermentation of proteins in the intestine may stimulate the magnesium-regulating centre in the brain (*mesencephalon* or *pons varoli*) and this may lead to the characteristic changes in the composition of the blood.

It is remarkable also that in other autointoxications of the animal body, which originate in the intestine, or in other organs, one observes changes in the composition of the blood, which in some respects show a similarity to those observed in grass tetany.

According to my observations this holds good, for instance, for the gastro-intestinal form of foot-and-mouth disease in cattle, a form of this disease which in the epizootic diseases of the last few years has become more and more prominent. We found similar disturbances of a biochemical nature in cases of autointoxication caused by excessive administration of new grass rich in protein and saltpetre, unripe apples, concentrates, etc. We also observed similar biochemical features of "disease" in para-tuberculosis—in which a disturbance of the intestinal function was also observable—and in some processes outside the intestine, in which large quantities of body protein are broken down, e.g., in the uterus following retention of the afterbirth.

Resistance of the Animal Body to Infectious Diseases

Finally, I would invite your attention to a problem to which biochemistry opens an, if possible, even wider vista than to the problems already discussed. I mean the general conditions for the setting-up of diseases caused by infection.

The setting-up of disease does not depend entirely on the characteristics of the pathogenic germs and on climatological factors, but, in no smaller degree, on the condition of the body exposed to infection. The problem of the resistance against infections, with which the body is provided by Nature, ought to be viewed in close relationship with the biochemical condition of the animal tissues. Consequently, it is dependent on the normal course of the metabolic processes. In an animal species, which shows no natural immunity, the spread to an individual may, with relation to the resistance against infections, be considered as fundamentally a variation in the activity of humoral, histogenous and phagocytary factors.

In the time allotted to me it is impossible to sum up the collective factors which—according to the experience of a great many investigators—may influence

the setting-up of a natural or acquired resistance. In so far as these factors, however, are of a biochemical nature, e.g., being related with nutrition, we can now show that the suitability of the tissue to serve as a matrix for the formation of new cells of the pathogenic germ, is of great importance. If the tissue is not in a condition to supply these micro-organisms with the materials which are necessary for their development, the tissues in question are unsuitable as matrices to the pathogenic germs, and infection becomes impossible, however pathogenic the germ may be in other circumstances. This is, in fact, the biochemical basis of modern chemo-therapy of sulphonamides and penicillin.

It is obvious that the biochemist asks himself in the very first place what the conditions are which create the possibility that in one animal a certain germ should be able to multiply whereas in another animal this is not the case. It is not improbable that this problem should be considered in connection with the possibility of the appearance of enzyme-action by which the material required for the development is formed from the chemical components of the tissues. It is highly probable that in most cases the acidity of the tissues cannot directly be an obstacle to the development of the micro-organism, for this does not diverge to any considerable extent from that which appeared optimally in cultures *in vitro*. However, indirectly a slight divergence from the acidity may be of importance, because it may influence the permeability of the cells, and certain enzyme actions, essential to the metabolic processes. When there exists complete impermeability with regard to bacterial poisons, serious injury to the interior of the cell is almost excluded.

Discussion and Summary

In this one hour I have tried to give you an idea of the task of the biochemist in studying vital processes. I have focussed your attention on the close relation between the biochemical condition of the tissues, and the physiological functions of the animal body.

In three biological problems, chosen by me, by way of example, which widely differ in character, viz., the biochemical disturbances of the " balance " in the animal body, autointoxication and the resistance against infectious diseases, the fundamental importance of the biochemical regulations have again and again come to the fore. I pointed to the similarity in biochemical respect, but also to differences in degree, which may very well be fundamental at the same time, between the various conditions. By the perfection of research methods we shall in the future have to try to trace the specific factors which, in the different circumstances in the body, make their influence felt.

In diagnosing biochemical disorders, a thorough knowledge is indispensable of the biochemical condition of the organism in the various animal species which live in different places and in different circumstances. A great deal of statistical work remains to be done in the field, which I should like to call the domain of geographical biochemistry. That biochemistry approaches here the field of geographical pathology in some respects will be manifest to anyone who is familiar with the comparatively great differences which may exist biochemically between the animal species, as well as among animals of one species or race, living in different circumstances.

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STUDIES ON EQUINE PURPURA HÆMORRHAGICA

Introduction

THE results to be presented in this series of five papers are the outcome of a preliminary investigation undertaken at the Royal Veterinary College, London, on three clinical cases of equine purpura hæmorrhagica, and require confirmation on a larger number of cases.

The researches were instigated by Professor E. C. Amoroso at the suggestion of Mr. V. Berwyn Jones following the appearance, early in 1947, of an unusually high number of cases in the London, Midland and Scottish Railway Stables. The work was carried out by the following members of the staff of the Royal Veterinary College: Messrs. P. M. Bennett, A. S. King and C. B. Murray of the Department of Anatomy, Mr. J. D. Biggers,* Dr. D. G. Harvey, Messrs. P. L. Ingram and R. H. Marchant of the Department of Physiology and Biochemistry. For providing full facilities for carrying out observations on the railway premises, the team are indebted to Mr. J. L. O'Connell, Chief Horse Superintendent and Veterinary Surgeon to the London, Midland and Scottish Railway, and Mr. V. Berwyn Jones, Horse Superintendent and Veterinary Surgeon to the London, Midland and Scottish Railway (London District), and to Messrs. E. Cotchin, H. D. Mills, P. Scott-Dunn, Miss G. Halley and Mrs. D. Z. King, of the Royal Veterinary College, for their assistance in the work.

REVIEW OF THE LITERATURE

Article No. 1

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No attempt will be made herein to review all the previous work on the condition. It is intended, however, to trace the earliest recognisable account of the disease as a separate entity, and then to give the more important details relating to ætiology and pathogenesis.

Before endeavouring to evaluate early descriptions, it may be of advantage to quote the definition of equine purpura hæmorrhagica given by Hutyra, Marek and Manninger (1946) in order that earlier accounts may be more readily contrasted with the present conception of the condition. These authors define the condition as "an acute, non-contagious disease of horses, probably arising from septic bacterial intoxication and characterised by extensive œdematous swellings of the subcutaneous tissues, with hæmorrhages in these and also in the mucous membranes and internal organs."

According to Hutyra *et al.* (1946), the essential and distinguishing features of equine purpura hæmorrhagica were first detailed by Hering (1841-1850). This statement, however, requires qualification, partly because two accounts were published in Europe at much the same period—namely, a very adequate description by Bouley (1842) and a paper by Hertwig in 1846 (quoted by Schmidt, 1918)—and more particularly because much earlier references exist in the English language.

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In searching the older literature for a description of any morbid condition, it is common experience that difficulties are encountered. One of these pertains to the fact that early authors sometimes confuse two or more distinct entities in a description of one disease; another is that some terms originally used are now obsolete and hence unknown to the present-day reader. This is at once apparent in tracing the early history of equine purpura hæmorrhagica, and is exemplified in the following descriptions, which might be diagnosed nowadays as purpura hæmorrhagica of the horse. William Gibson (1680?-1750), in 1735, described a " putrid fever " accompanied by small hæmorrhages, and, in 1810, John Lawrence (1753-1839)[1] stated that dropsy may be due to some antecedent disease. Similarly, at various times the disease has been included under the names *l'anasarca idiopathique du cheval* (Bouley, 1842), *putrid fever, horse typhoid* or *anthrax;* it has also been allied to *scarlet fever* in man (Hutyra *et al.*, 1946).

It was the veterinarian John Field, Jnr.,[2] who left what appears to be the earliest definite accounts of the disease,[3] which were included in a book published posthumously. It is described accurately, first under the name *pyrecchymosis,* and later under the name *purpura hæmorrhagica;* the earliest date of the former was September 15, 1828. In the same book (Field, 1843) another document appears, dated October 28, 1839, which is, most probably, the draft of a paper giving a general account of equine purpura hæmorrhagica; in view of its historical interest, extracts from this paper are quoted below.

(October 28, 1839)

III.—PURPURA HÆMORRHAGICA.

So designated by Dr. Willan, where petechial spots appear on the skin, with or without fever.

Affects the skin, mucous membranes, cellular tissue, parenchyma of internal organs, as lungs and kidneys; also issues from the brain, from between the coats of the intestines, and from the mucous cavities of the body.

Symptoms.—Effusions beneath the skin, of irregular form, on the thighs or forearms, or under-part of abdomen, gradually or suddenly increasing; petechial spots on the Schneiderian membrane; swellings of nose or lips; ecchymosis of conjunctiva; painful tumefaction of thighs or forearms, occasioned by similar extravasation beneath the fascia, or in the cellular texture of muscles, occasioning limited motion, incapability of flexing the legs sufficiently to rise when down; sanguineous exudation from skin: in this state, much constitutional disturbance; accelerated respiration; partial sweating; frequent, wiry, or full and strong pulse; scanty excretions. As the disease advances the swellings become confluent; greater depositions of lymph, as well as blood, take place in the thighs and nose, and under the eyes; a sero-sanguineous discharge takes place from nostrils; the Schneiderian becomes nearly black, the membranes not affected, or the buccal rather paler; the respiration is snuffling, from effusion into the nostrils; the pulse becomes more frequent and feeble; the horse paws, or looks back, or anxiously turns his head from side to side; sometimes small portions of blood are voided from the nostrils, or with the urine, but these are not common in the horse; great debility quickly supervenes; the animal totters if made to walk about; his blood becomes thin and pallid; it separates very rapidly when drawn, and does not, according to Mr. Lane, exhibit the normal tendency to assimilate its chylous particles. The urine, in Mr. W's horse had much albumin in it, was ropy, and coagulated with nitric acid and heat. The skin is often distended, sometimes so much so that, through flexing, very large ulcers are occasioned.

Duration.—From 3 to 7 days, in fatal cases: if the horse survive that period, though the circumstance is favourable, it may recur, and prove fatal by deposits in vital organs, or by gradually exhausting the vital powers.

Morbid Appearance on Dissection.—Dark or black blood effused beneath the skin or fascia, or in the fibres of muscles, giving a dark modena or purple or black colour to the portions in which it occurs, and a lighter hue to the other parts of muscles; much effusion of lymph in contiguous structures; deposits more extensive in the more quiescent muscles, as the pectorals and psoæ, if the horse remains quiet; also, between the coats of that portion of duodenum tied to the capsule of Glisson, terminating abruptly, where it is loosely held by

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mesentary before crossing the spine; and also at the pylorus; ecchymoses on the pleura, and in the substance of the lungs; slight blush in the bladder, and spots of elevated ecchymoses in bladder and ureters, or inflammation and deposits in the coats of the intestines, either in the colon, cæcum, or small intestines; the heart is affected; deposits of blood, various, upon the cerebrum and cerebellum.

Pathology.—(1) An increased tenuity of the blood; (2) dilatation of the mouths of the capillaries, admitting natural blood to pass through them; (3) tenderness of the coats of the vessels, giving way from the ordinary impetus of the blood; (4) increased impetus, rupturing healthy vessels; (5) obstruction in the capillaries; (6) two or more of these causes combined. Still, the universality of the disease does not allow of the proper explanation of the phenomena from either of the above causes, and the more rational mode of explaining it seems that which refers to an alteration in the condition and vital properties of the blood.

Exciting Causes—Pre-disposing Causes.—Debility, induced by previous inflammatory disease, either severe or mild; poor living; frequent irritation: it occurs, also, without any assignable cause.

Prognosis.—Must be guarded, and can only be favourable when the fever has abated—when the swellings are confined to the limbs, not attended with difficulty in motion—when symptoms of internal mischief are absent—when there is plentiful diuresis: but if the urine be scanty, ropy, voided in small quantities; if there be much painful distension of the thighs from effusion beneath the fascia; if there be much extravasation about the nose and head, and effusion beneath Schneider's membrane, etc., the prognosis is unfavourable; and, moreover, if symptoms of internal disease exist.

Remarks.—A disease of the highest interest in a pathological point of view, and requiring more investigation, and seemingly referrible to a morbid condition of the blood and fluids

This is the earliest general account of the disease which we have found, and it does not appear to have been quoted subsequently in the literature. Also, it is a particularly lucid exposition of the disease when one considers the limitations of veterinary knowledge at that time. It seems that, from a clinical point of view, the disease was recognised as a distinct entity in this country by 1828. It was not until after 1843, when Field's work was published, that the condition was recorded extensively by other practitioners. Unlike Hering, however, Field failed to point out the non-contagious nature of the disease.

After a careful study of the literature, it is obvious that very few systematic investigations of this disease have been undertaken. When this work was commenced, only one really informative paper appeared to exist, that by Wittman and Contis (1924). Recently, however, another extensive paper has been published (Jennings and Highet, 1947).

In recent years, the majority of the communications on equine purpura hæmorrhagica have been case reports (Stanton, 1943; Begg, 1942; Narsaya, 1940; Aehle, 1939; Kalkarni, 1938; Parmaiki, 1938; Sharma, 1938; Editorial, *Cornell Vet.*, 1937; Leistner, 1937; Gooch, 1937; Wessels, 1934; Kramer, 1929). There is also a discussion of the condition by Davenport (1937), and an editorial article in "Veterinary Medicine" of 1942. All these communications throw little light on the problems of ætiology and pathogenesis.

The various methods of treating equine purpura hæmorrhagica have been reviewed by Schmidt (1918), who provides a very extensive bibliography predominantly of the continental literature. He classifies the methods employed, up to that date, into seven groups according to the therapeutic changes deemed desirable to combat the disease. Assuming some degree of rationality behind these measures, an analysis of this classification can provide some information on the early views with regard to the ætiology and functional pathology of this condition. The classification of Schmidt is as follows:—

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(1) To destroy the supposed causative agent in the alimentary canal.

(2) To neutralise the supposed poison in the blood or organs to allow its removal by increased organ activity.

(3) To destroy possible pathogenic organisms in the blood or organs by drug administration.

(4) To employ serum therapy.

(5) To reduce blood volume and alter the blood pressure.

(6) To alter the state of the vascular walls.

(7) To restore the blood volume.

Consideration of these methods show that 1-4 are aimed at eliminating the primary cause, whilst 5-7 are purely symptomatic treatments. The latter provide information on the early knowledge of functional pathology and appear to be derived from speculation on clinical signs and not based on quantitative observation of functional changes which occur in the disease. On the other hand, the former shed some light on the early views as to the ætiology of the condition.

The question of ætiology was first discussed in the second half of the 19th century. An early suggestion was that the condition arose from some toxic substance very slowly produced, from an unknown source located in the intestinal tract (Hertwig, 1846, quoted by Schmidt, 1918). As a result of this hypothesis, a variety of intestinal medicaments were administered orally in the hope of combating the "causative agent" at its site of production, and so preventing its absorption into the circulation.

Similarly, the view was held by some that the disease was due to a poisonous substance, of an unknown nature, present in the blood or organs. Thus, Dieckerhoff (1887) used iodine intratracheally in an attempt to neutralise the "hypothetical poison." This view also led to the administration of a variety of iodine compounds, though their efficaciousness did not go unchallenged (see Schmidt, 1918).

Hering (1841-1850) and Haubner (both cited by Hutyra *et al.*, 1938) showed that the disease could not be transmitted from an affected to a non-affected animal by the inoculation of various secretions or blood; also, Arloing (quoted by Hutyra *et al.*, 1946) demonstrated that transmission did not follow direct blood transfusion. In addition, it was known that the condition was often secondary to other infections of various types. Thus, Dieckerhoff (1887) suggested that the condition was the result of toxin production by micro-organisms in the purulent or necrotic foci left by a primary infection. The work of Lignières (1895) showed that, although streptococci would not produce the disease, they were usually associated with it. Mouilleron and Rossignol (1898), and Cormier (quoted by Hutyra *et al.*, 1946) also showed that streptococci are concerned. The main evidence, adduced by this French school to show the importance of streptococci, appears to be based on their claim that antistreptococcal serum is efficacious in combating the condition. Taubitz (1936) also had some successes, though some failures, in treating the condition with an antiserum against *Streptococcus equi*. A similar fact is that in some cases certain sulpha drugs have been claimed to effect a cure. A full

reveiw of the bacteriological work carried out mainly in France at the end of the last century has been published by Drouin (1906).

Cadéac (quoted by Hutyra *et al.*, 1938) regards the condition as an intoxication occurring in debilitated animals as the result of a vasodilatory toxin produced from different bacteria. Hutyra *et al.* (1946) suggest that the disease is possibly due to injury of the blood vessel walls by a circulatory toxin which reduces their elasticity and resistance. This was also suggested by Bemelmans (1935), who believed that a toxin was elaborated by diplo-streptococci, which had a neurotropic action, causing atony of the vasomotor nerves with resultant dilatation and hæmorrhage. Although some of the expressions used by these older workers have little or no meaning and are incapable of precise definition, their general conclusions appear to be that the disease is caused by bacterial toxins (probably from streptococci) elaborated in purulent or necrotic foci—a legacy of some primary infection —which enter the circulation and impair the normal functioning of the vascular walls.

Several workers hold the view that the disease is of an anaphylactic nature. This has been suggested by Marek, Ritzenthaler and Greig (all quoted by Hutyra *et al.*, 1946), Scheltenkow (1935) and Davies (1946). Marek produced the condition experimentally by the injection of a series of doses of streptococcal extracts one month after a series of sensitising doses. Schmidt (quoted by Hutyra *et al.*, 1938), however, while incriminating bacterial toxins, states that a repeated dose of toxin is not required. Ritzenthaler produced the condition, in a similar manner to that of Marek, by the injection of egg-white; he then transmitted the condition from an affected to a previously non-affected animal. This work is interesting, although contrary to the earlier findings of Hering and of Haubner. Unfortunately, the brief mention of these results by Hutyra *et al.* does not give any information on the method of transmission employed. It may be that repeated transfusions from an affected animal might result in transmission of the disease. In this connection, the case report of Gooch (1937) is relevant, where an instance is described in which a suckling foal succumbed to the disease after its mother had been affected; this may have been due to natural passive transmission. Scheltenkow (1935) describes the condition occurring in serum horses; here, again, the obvious hypothesis to hold in explanation of the disease is that it is anaphylactic in origin. Davies (1946) regards the condition as anaphylactoid in nature, probably an histaminosis.

The current views on the ætiology of equine purpura hæmorrhagica still fail to provide a proper understanding of the condition. Broadly, two main theories have been held: (1) that the disease is the result of chronic intoxication, and (2) that it is of anaphylactic origin.

The purpuric conditions of man have recently been reviewed by Whitby and Britton (1946). These conditions have been classified using changes in the blood clotting picture as a basis of distinction. Neglecting purely symptomatic purpuras, the diseases can be grouped into two major categories: (1) those in which there is a disturbance of the blood clotting mechanism (essential thrombocytopœnia), and (2) those where the blood clotting mechanism is normal (the "vascular group"). The ætiology of these conditions is not understood; the former is

associated with a thrombocytopœnia, while the latter group is connected with anaphylactic phenomena.

Very few papers exist on the pathology (other than the morbid anatomy) of equine purpura hæmorrhagica. A few observations have been published on the blood and urine of affected animals.

Mielke (1913) studied the blood picture in four cases of equine purpura hæmorrhagica. His results show a leucocytosis and high red cell counts with sudden and rapid fluctuations. Wittman and Contis (1924) carried out serial hæmatological observations on nine affected animals. They reported a progressive anæmia, except in case IX, which died in the initial stages of the disease. Although they do not comment on the fact, their published figures, in certain animals (cases III and V), do show fluctuations in the red cell counts with corresponding changes in the hæmoglobin values of the blood. These workers also describe a leucocytosis, and in several cases the presence of many blood platelets. Bellocq and Louf (1943) have reported findings on the urine and blood at one stage only during the course of the disease. Chemical observations on the blood of one case, after death, were made by Smith (1887). Jennings and Highet (1947) have also made serial hæmatological observations on ten cases. They describe a severe anæmia, leucocytosis (mainly neutrophilia, and a high monocyte count), and an increase in the icterus index.

It has been suggested, though never investigated, that nutritional factors may have a role in the pathology of this disease. A deficiency of ascorbic acid has been incriminated by Kröcher (quoted by Hutyra *et al.*, 1946); and Hughes (1938) has reviewed the relation of ascorbic acid and the P-factor to purpuric conditions, suggesting that they may have some importance in equine purpura hæmorrhagica.

In view of the shortage of information on the pathology of this condition, it was considered that the results we have obtained are worthy of publication, since they serve the useful purpose of indicating lines of further research into the nature of this disease—"a disease of the highest interest" (Field, 1839). Our results will be presented in subsequent papers.

(1) This well-known author was neither a veterinarian nor a physician, but may have acquired his knowledge through his association with Sainbel (1750-1793)—see Smith (1924).

(2) John Field, Jnr. (1800-1839), was one of the two sons of the eminent veterinarian John Field, Snr. (1768-1833). The former left only a few publications before his death, but his notes and some case records were published posthumously in 1843 by his brother, William Field. We are indebted to Mr. H. D. Mills of the Department of Anatomy, Royal Veterinary College, for drawing our attention to this work.

(3) Sir Frederick Smith (1924) stated that Professor William Dick (1793-1866) was the first to describe the condition and to suggest the name *purpura hæmorrhagica*. We have been unable to trace any publication of Dick dealing with the disease; furthermore, as has been already shown in the text, John Field described the disease accurately in 1828. These two facts together would seem to dispose satisfactorily of the suggestion that Dick was the first to describe this entity. Concerning the introduction of the name *purpura hæmorrhagica*, there is much circumstantial evidence that Field should be given the credit. Prior to the publication of his notes in 1843 (Field, 1843), no use had been made of the name *purpura hæmorrhagica*. Yet there is no doubt that the condition had been recognised as a distinct entity. For example, Percivall (1792-1854), in 1834, described a remarkably similar disease under the name *scarlatina*, whilst later, in his book "Hippopathology" (Percivall, 1834), he described it under the name *morbillous disease*. And similarly, a disease, which was indisputably purpura hæmorrhagica, was alluded to as *anasarca* by Hales (1836). The exact words of this author were: ". . . more particularly in those anasarcous swellings of the limbs or abdomen which ever now and then succeed to strangles or catarrhal affections, and

which are sometimes accompanied by red or purple spots in the lining membrane of the nose." After 1843, case records of purpura hæmorrhagica appeared under that name in the literature (e.g., Cox, 1848; Mannington, 1848; Haycock, 1850). This suggests that it was Field's book which drew the attention of practitioners in this country to this disease under the name *purpura hæmorrhagica,* rather than a prior publication of Dick. Furthermore, Dick was the editor of the "Veterinarian," in which Percivall (1834) introduced the name *scarlatina.* It is surprising that, if Dick had suggested the name *purpura hæmorrhagica,* comment was not made. Moreover, in the same journal in 1843, the book of Field was reviewed; in this review the following extract appears: ". . . we think Mr. Field's the more appropriate appellation. . ." It thus seems that it is to Field that credit is due for (i) clearly describing the disease for the first time in this country, and (ii) introducing the name *purpura hæmorrhagica.*

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A SHORT NOTE ON THE IDENTIFICATION OF THE ORGANISMS FOUND IN BOVINE MASTITIS IN U.S.A.

By H. F. FARRAG, B.V.Sc., M.V.Sc.(Cairo), Ph.D.(Kansas)

MILK samples were taken aseptically in test tubes, and after discarding the first two streams, a diagnosis was made by:—

(1) *Microscopical Examination of Incubated Milk*:

Samples were incubated overnight at 37° C., then well shaken, and a small quantity was removed by wire loop and smeared on a slide. The slides were allowed to dry, immersed in xylene for two minutes, dried and immersed in 95 per cent. alcohol, dried and then again stained with methylene blue.

(2) *Blood Agar Plate*:

The fresh sample was shaken and 1.1 ml. of milk removed, 0.1 ml. of which was placed in a sterile Petri dish; the remainder, 1 ml., was diluted in 99 ml. sterile water and 1 ml. of this dilution placed in a second dish, so that the inocula would correspond with 1 ml. milk diluted 1 : 10 and 1 : 100 respectively. Into each dish was poured about 10 ml. of melted proteose—peptone agar cooled to 45° C., containing 5 per cent. defibrinated sheep blood. The plates were incubated for 48 hours at 37° C. and examined. Colonies from the plates were transferred to proteose—peptone broth for further examination.

For distinguishing *Streptococcus agalactia* from other streptococci, the following differential tests were used:—

(1) *Sodium Hippurate Test*:

The procedure described by Mackie was followed. The organisms were grown in broth containing 1 per cent. sod. hippurate for 5 days. To 1.0 ml. of the supernatant fluid of the culture was added 0.4 ml. of 12 per cent. ferric chloride solution containing 0.25 ml. concentrated hydrochloric acid. If an insoluble precipitate was formed, this would indicate *Streptococcus agalactia.*

(2) *Esculin Test*:

A negative reaction to esculin indicated *Streptococcus agalactia.*

(3) *Litmus Milk Test*:

In the case of *Streptococcus agalactia,* milk was coagulated in about 48 hours without reduction of the litmus.

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Morphological Appearance: In the infected milk, the organisms were found in chains, but not always long chains, as most references mention; in some cases the chains were found to be very short.

Growth in Proteose—Peptone Broth: Growth occurred only in the bottom of the tube and was granular and flocculent; the remainder of the tube was almost clear. Growth was more satisfactory in Bacto Tryptose Phosphate Broth.

Appearance on Blood Agar: Most references state that strains of *Streptococcus agalactia* may produce four distinct types of growth on blood agar—

(1) Narrow-zone hæmolytic colonies.
(2) Broad-zone hæmolytic colonies.
(3) Green hæmolytic colonies.
(4) Non-hæmolytic colonies.

In this work, only the first two forms, i.e. the narrow-zone hæmolytic colonies and the broad-zone hæmolytic colonies, were found. Moreover, the latter were not abundant, the majority being the narrow-zone type, producing a zone of hæmolysis about 1 mm. in diameter. Of the 60 strains of streptococci examined, 10 were atypical, i.e. not *Streptococcus agalactia, dysgalactia* or *uberis*.

In the case of staphylococcus infections, the organisms were identified by:—

(1) Hæmolysis: There was a marked zone of hæmolysis when the blood agar plates were incubated for 24 hours or 48 hours.
(2) Coagulase test: Strains coagulated blood plasma by adding one drop of the broth culture to citrated plasma and incubating at 37° C.
(3) Pigmentation: Strains were orange-yellow colour on agar slants.

The combination of these two methods, i.e. microscopical examination of incubated milk and blood agar plating, was found to be very efficient in the diagnosis of mastitis.

* This work was carried out in Kansas State College, in the Department of Bacteriology, under the supervision of Professor L. D. Bushnell.

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BOVINE TUBERCULOSIS: TOTAL ERADICATION AS AN OBJECTIVE

A Review By J. T. EDWARDS, D.Sc., M.R.C.V.S.

"If we can create Attested herds at the same rate as in 1938-39 *we shall have practically eradicated bovine tuberculosis within* 30-40 years" (our italics).

On this note of hope and faith ends the remarkable little book before us now for review.*

As its reviewer, we shall discharge at once the task customarily imposed at the end of criticism. In full charity towards the author we must say that there are in the book some distinct imperfections. These come from a restricted personal experience with many phases of the subject treated. Be it said at once, however, that hardly anyone in the veterinary profession at the present day can be expected to be fully familiar with every phase of the subject as designated. He has succeeded, nevertheless, in writing an eminently readable and, on the whole, trustworthy synopsis upon it, which, at the moment, is sadly needed, not only by veterinarians, but also by the several other interests which are directly or indirectly concerned. Through a combination of sound historical sense, care in collecting and sorting the recorded facts, good acquaintance with the experimental method, and keen critical judgment, the author has been well rewarded, in our opinion, for his pains and courage. He has presented, for the first time, the short guide-book now greatly needed to point out surely the goal of an endeavour, the undertaking of which has at long last impressed the intelligence and stirred the conscience of the British public. Until then, nothing could be done.

It is to the credit of the British veterinary profession that it has never ceased to advocate, as the only course likely to solve permanently the grave problem at issue, the putting into operation of such measures as are now backed by State legislation, with the setting up of the consequent services necessary to give effect to them. The problem at issue is a grave one, whether looked at from the public health standpoint or from, what is even more important and in many ways very different, the agricultural standpoint. We shall not pause to cavil at Francis's assessment of the gravity, but content ourselves with saying that, in the light of the evidence, such as that is (or, rather, as that was at the time of his writing), it is a fair one. The evidence is now fast growing, and the assessment will stand in need of revision even at the time of present writing. If anything, however, the accruing evidence merely serves to clarify further the objective as perceived by Francis and strengthen the case for its attainment, perhaps in a time much shorter than he has estimated.

It had been McFadyean's apprehension in the official campaign that was undertaken to eradicate glanders, which came about after faith was placed in mallein as a diagnostic aid by British veterinarians, there would occur a persistent drag in reported cases, succeeding an abrupt initial fall in the number of out-

* Bovine tuberculosis, including a contrast with human tuberculosis. By John Francis, B.Sc., M.R.C.V.S., 220 pp. With 36 figs. and 21 tables; 406 refs. London: Staples Press, Ltd. (Price 25s net).

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breaks. Happily, and surprisingly to him, that was not how the infection fared. After a sharp fall, the infection, as it were, lost foothold, and in 1913 vanished for ever.

It would be too much, at this stage, at any rate, to predict a similar outcome with bovine tuberculosis as with equine glanders, but all the same, "one never can tell."

There are several things about the two infections, many of which we well know and need not here be elaborated, that are different; and so the two campaigns may not turn out to have parallel courses.

But there is one overriding factor that operates in both and must be stated in as plain language as we can command to our use. It is the degree of public apathy that must be overcome. In the case of glanders, thanks in particular to the professional zeal of the late William Hunting and to the co-operation of a relatively enlightened body of the public that was interested, namely the large horse owners of London and other cities, that obstacle was not very difficult to overcome. In the case of bovine tuberculosis, despite the present beneficent legislation, that obstacle is incomparably more formidable, largely because of the greater intractability of the more numerous and varied sections of the public that are interested. Nevertheless, it has to be faced, and faced resolutely too. Let us make no mistake about that. The veterinary professions, acting in concert with the administrations, in other countries (Finland, Norway, Guernsey, U.S.A.) have faced it, and succeeded in their endeavour. It will be to the shame of the British veterinary profession if, in the light of the evidence concisely put before it and well digested as it is in the little book before us, it does not acquit itself equally creditably.

The book, as we are told by Dr. Innes in an admirable foreword, owes its origin to an invitation from the Editors of *Tubercle*, the Journal of the Tuberculosis Association, to write a review on bovine tuberculosis. That, wisely, Francis maintained, could not properly be attempted until the evidence was displayed fairly, as it has not hitherto been. The monograph thus resulting having been accepted for publication, the editors invited two veterinarians, namely, J. N. Ritchie, on the epidemiological side, and J. T. Stamp, on the morbid morphology side, to write a review which would incorporate criticism of the monograph. (*Tubercle*, 1948, *29* (2 & 3), 34-40, 61-66). No better choice of competent reviewers could be made. Concluding their review and dealing with the brightening prospects of "area eradication," for which there exists authority under the Agriculture Act of 1937, and with its practicability in the light of U.S.A. experience, the authors give support to Francis's main thesis, as quoted at the beginning of the present review, in their words: "*There is therefore good reason for the belief that tuberculosis can be eradicated from the cattle of Great Britain* (our italics).

If anything, the reviewers' language errs on the side of excessive moderation. There is, to our mind, no need to be hesitating in the choice of words. The British veterinary profession has to its credit, as we have said, that it has pressed on the attention of the public the promulgation of measures resting on such a belief.

Confidence in that belief has come largely through long experience in the successful extirpation of several diseases, in their time formidable, tempered with the salutary warning given in the case of some diseases where attempted extirpation has not proved practicable. But it has also come in no small part from paying heed to wise counsel when it has been available, as it was providentially from the very beginning (if as a beginning we reckon Koch's discovery of the tubercle bacillus, in 1882, which clenched the paramountcy of the role of infection in tuberculosis) in the teachings and writings of a great master of his subject, the late Sir John McFadyean. We would like to see four of his addresses, together with Ritchie and Stamp's review, added somehow as appendices to Francis's monograph, namely, first, that given before the N.V.M.A. Congress at Plymouth in 1900, in which he warned his veterinary colleagues that the problem of bovine tuberculosis was not nearly so pressing from the public health standpoint as it was sometimes represented to be and against the dangers of overstressing its importance in this respect; secondly, his criticism of Koch's address on the duality of human and bovine tuberculosis at the British Congress for Tuberculosis in 1901, in which he pointed out to the world that despite Koch's conclusions, which he proved fallacious, bovine tuberculosis was of very real significance from the public health standpoint; thirdly, his inaugural address at the opening session of the Royal Veterinary College, London, in 1913, in which he commented upon the first launching of measures of control by the State and their meaning to the veterinary profession; and, fourthly, his opening address, as President of Honour, at the Second International Congress for Microbiology held in London in 1936.

He (McFadyean) had then, in 1936, behind him sixty years of experience as veterinary teacher, investigator and counsellor, and was an old man of 83. Surveying the progress that had been made since he was present at the first Congress of a similar kind, namely the International Congress of Hygiene and Demography, in 1891, in London, he was happy to relate that in the intervening 45 years, through the application of the stamping-out method, bovine pleuropneumonia, rabies, and glanders had been eradicated, and foot-and-mouth disease had, on many occasions, been stamped out, though permanent freedom from it could not be assured.

" Great credit," he continued, dealing with bovine tuberculosis, " is due to the Ministry of Agriculture and its present distinguished President (Mr. Walter Elliott) for the plan of gradual eradication recently begun, but since it is not compulsory its effect will be slow, and meanwhile the infection of human beings with bovine tubercle bacilli in milk will continue.

" The principal obstacles to eradication appear to be expense and apathy on the part of the public. These difficulties have always arisen in connection with efforts to stamp out contagious diseases of animals that are not rapidly fatal, and in the present case the greatest of them is apathy. The general public are not convinced that there is any serious danger of children becoming infected if what is called clean milk is obtainable, and the family doctor is sometimes of the same opinion.

"An increased effort to bring the facts in this connection home to the public is greatly to be desired.

"I am, myself," he ended, "peacefully minded, and would not wilfully say anything calculated to excite tumult or rebellion, but I wish the people would arise and demand that this continued infection of human beings with a preventable disease must now stop.

"Alternately, we may say that bovine tuberculosis, like the poor, will be always with us."

Since those words were uttered, a second world war has come about to stay the progress which was being so well achieved immediately before it, but none the less it came about to arouse the public out of its apathy in more ways than one, and particularly in respect of incurring expenditure upon such vital matters to its existence as its good health and its sources of essential food. The review forthcoming from Ritchie and Stamp furnishes us with data that were not accessible to Francis, boding well that the goal is coming now more clearly within sight of achievement.

We shall not trouble to comment upon Francis's attempt to contrast bovine with human tuberculosis. That has been adequately dealt with by Stamp. He (Francis) is evidently a little out of his depth here, as the present reviewer himself would most certainly be, having had no experience in the study of the human disease. That there must be wide divergencies in the disease as it affects the two species is evident. The veterinary pathologist, well acquainted as he is with the considerable divergencies in the picture as presented by three zoologically fairly closely related species, namely the ox, horse and pig, not to mention the more distantly related ones, such as the dog and cat and the various laboratory mammals, and even more so the fowl, would not be surprised to learn that there is great divergence from his common experience when it comes to the picture presented by tuberculosis in the human subject.

Those who saw things develop from the beginning were perhaps in a better position to appreciate all this as it gradually unfolded itself before their eyes. The great pioneers in the advancement of our knowledge upon bovine tuberculosis, such as Theobald Smith, in U.S.A., Bernard Bang, in Denmark, and John McFadyean, in Britain, had had themselves a medical training, though that was probably, in the outcome, merely fortuitous, inasmuch as they disciplined afterwards their outlook upon their problem towards the objective, veterinary, one, and far away from that of the physicians who devote their time to the clinical study of human tuberculosis. Conversing with these physicians, it is strange to find how very little, with the rarest exceptions, they appreciate the problem as it confronts the veterinarian in his own domain. The very rare exceptions, in our experience, are those who have devoted a large part of their lives to experimental research upon tuberculosis, and we are happy to find full assurance that the investigations now in progress to discover what are the possibilities of vaccination are in such safe and careful hands. Somehow, however extensive may be the experience of the worker upon any phase of the tuberculosis problem, we

find there is something lacking in his mental equipment for proper assessment unless he has the inclination for, and acquired proficiency for about ten years or so in, experimental research upon tuberculosis as a main occupation; for, in tuberculosis research, one finds, the technique and tempo of the work breed a kind of perspicuity that is not engendered in most other forms of experimental research.

It is here, in a few places, that the otherwise very fine review by Ritchie and Stamp betrays signs of being somewhat wanting. Dealing, for example, with the "single intradermal comparative test" (*i.e.*, using both mammalian and avian tuberculin simultaneously to compare the sensitivity of an animal to each and thus deducing the probability of mammalian-type infection), they say: "When properly interpreted on a herd basis the comparative test is probably the most accurate test available; it is of much less value when applied to individual animals." We can grasp their meaning well, but there is just a little danger that as expressed in this way their words may shake the confidence of the uninitiated.

The truth, as we can see it, is something like this: (1) For about fifty years, in spite of all limitations, most of which are well known, and the many minor refinements that have been made and are still to be made in its preparation and application, we have had reason to repose faith in tuberculin for the diagnosis of tuberculosis in cattle, and as in nothing else. (2) For the latter half of that period we have had reason to repose faith in the intradermal method of testing with tuberculin; consequent upon the faith thus reposed in this form of testing, bovine tuberculosis has been eradicated from extensive areas in the world in which it was formerly prevalent; with better understanding of the problem confronting us in Great Britain, and with the necessary authority for action and the requisite facilities duly granted to us, we apprehend no insurmountable difficulty against achieving a similar end in this country. (3) Cattle sometimes are infected with certain congeners of the bovine type of tubercle bacillus, which may confuse diagnosis when the intradermal test using tuberculin prepared from mammalian-type bacilli is alone applied; common congeners are reckoned among bacilli of the avian type and of Johne's disease; it is now deemed prudent to test intradermally simultaneously with tuberculin prepared from avian-type bacilli, which is destined to reveal infection by them and so to enlighten diagnosis.

Doubtless in was in the minds of the Editors of *Tubercle* that medical workers needed much enlightenment upon the disturbingly different aspects of bovine tuberculosis, now that State action on a determined scale is in process of development and the co-operation of the medical profession, no less than that of every other interest, including particularly the agricultural interest, is highly desired.

This would explain Francis's intrepid sortie into a domain that is not familiar to veterinary workers. Its strangeness to the latter is apparent if only one glances at the numbers of *Tubercle* in which Ritchie and Stamp's review appears.

It is fatally easy for the one profession to castigate the other for shortcomings when the one is not in possession of the observational evidence currently presented to the other. Thus, in a striking address given in 1923 (the

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Dick Centenary address*), McFadyean extolled the veterinary profession for not having been led so long into serious error in advancing heredity as playing a predominant role in the causation of tuberculosis. It is easy for us now to appreciate why even an earnest medical worker could be misled in a way that would not lure the veterinary worker. The evidence of the tuberculin test, it is thought, reveals that about 90 per cent. of the human population sooner or later in life become infected with tuberculosis. Providentially, in the great majority, the primary lesions thus set up regress to complete recovery. Through a concatenation of circumstances, of which hereditary predisposition seems to rank foremost, the lesions may progress, often long after the date of initial infection and as the result of exogenous reinfection of a subject already sensitised by an antecedent primary infection, to a state that is phthisical, and, only too alarmingly, fatal. Sensitivity to intradermal tuberculin seems to give an indication of the proneness of the individual to a phthisical issue; for, in some of the highly susceptible races of mankind, such as are found among some African and Asiatic natives, a response to tuberculin after infection may be observed after inoculation of tuberculin at a 1/1,000,000 dilution; whereas, in the more resistant races or individuals, the concentration needed to detect infection in much lower—about 1/10,000; while, again, below that concentration—1/100 to 1/1,000—if the individual *fails to react,* an indication is assumed to be obtained that the individual is *not* infected and therefore lies in danger of becoming, perhaps, seriously, infected and so stands in need of artificial infection, with BCG or similar vaccine, to "immunise" him, against ever-present risk.

The long phase of sensitisation to reinfection after an initial infection is

* McFadyean, J. (1923): *J. Comp. Path. and Therap., 36,* 243:—

". . . Progress in both the sciences (medical and veterinary) is said to have been hindered by failing to recognise that they are branches of the same great subject, viz., the study of diseases. In so far as this contention implies that the pursuit of knowledge regarding the diseases of the domesticated animals by veterinary pathologists has been made in a 'water-tight compartment,' it is quite unfounded. It would be much nearer the truth to say that veterinary pathology during the first half of the century that we are dealing with was retarded because it was too much influenced by the current beliefs regarding human diseases. Examination of the literature of that period will convince anyone of the truth of this statement. In many cases erroneous conclusions were formed with regard to animal diseases because of their supposed analogy with diseases of man, and because it was not sufficiently recognised that resemblances between different diseases in man and animals, or between disease in different species of animals, are of slight importance from the practical point of view.

"Many illustrations of this could be given, but one may suffice. It was from human pathology that veterinary surgeons adopted the view that bovine tuberculosis is a hereditary disease. That view is now known to have been erroneous with regard to human tuberculosis, although the frequent occurrence of what may be called family tuberculosis in man appeared to admit of no other explanation. But there never was similar evidence to suggest that the disease in cattle was hereditary, and proof to the contrary was easily found when it was sought in the proper way.

"The greatest progress regarding animal diseases has been made in the last fifty years, during which period veterinary pathology has, so to speak, commenced to stand on its own legs. The notion that it would be possible to create a class of men with an intimate knowledge of both human and veterinary pathology is a fantastic one, and it can hardly have occurred to anyone who has made himself master of either. In both professions it is specialisation that has done most to increase knowledge, and it is by the same process that we must seek to advance. If the contention were that it would be better if veterinary surgeons knew more about human pathology and doctors knew more about animal diseases, no-one would deny its desirability in the abstract, but while human life remains at its present span the necessary extension of either the medical or the veterinary curriculum is not likely to take place. . . ."

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curious in tuberculosis, and its significance is beginning to be appreciated by veterinary workers, no less than it has been for some time by medical workers.

At a time when heredity was mistakenly assumed to play generally a preponderant part in the pathogenesis of clinical tuberculosis, it is understandable that pioneers like McFadyean should preach impressively that, without infection, tuberculosis, as such, could never be set up. This is, of course, in the light of our better knowledge, the truth. And, as regards the problem that confronts us here now in Britain, which is to eradicate tuberculosis from our cattle herds with all speed and at all costs, nothing else about the disease as it affects the bovine need vex us.

When, after the use of tuberculin, the bovine is declared infected, the only course to take, to attain our objective, is that of Rome towards Carthage, when in quest of dominion over her rival, and that is, it "*must be destroyed*"—or, at any rate, put out of harm's way.

When, on the other hand, the human subject is found infected, at whatever stage, the only course that is open to follow, and, indeed, ought to be followed in view of the ubiquity of human-type infection, is that of the Christian gospel towards sinners, and that is, it "*must be saved*"—though how it is to be saved, except through the mercy of Providence, medical science has as yet no certain way of telling us. That may, however, come soon, and perhaps suddenly, and may be from advances in knowledge within the comparative field.

The late William Bulloch, the historian of bacteriology and friend and ardent admirer of McFadyean (incidentally recommending him for the first award of the Weber-Parkes prize for outstanding work on tuberculosis) states in his historical introduction to the chapter on Tuberculosis in the Medical Research Council's *System of Bacteriology* (1930, Vol. 5, p.154): "The decade following Koch's work (1882, 1884) created a voluminous literature, and was largely occupied in filling trivial lacunæ, but everywhere his observations were confirmed in all essential details."

Bulloch had some of the weaknesses of a hero-worshipper, for otherwise he could have said that the decade that followed upon that decade again, so far as the medical profession was concerned, was an inglorious one. It was heralded by Koch's discovery of tuberculin (1890) and ended with his famous pronouncement at the London Congress (1901), already mentioned, upon the distinctiveness of the common forms of human and bovine tuberculosis (which had already been noticed by the French worker, Villemin, as far back as 1866, and had been explained, in the light of ascertainable bacteriological differences, by Theobald Smith in 1896 and 1898).

Whereas veterinary workers were not slow to discern the real and great utility of tuberculin, which was as a much needed and indispensable aid to diagnosis, medical workers temporised dangerously for long on the possibilities of using it as a remedial agent. The present reviewer well recalls, as recently as 1913, working abroad with a group of young highly qualified English medical graduates (that is, "highly qualified" in the sense that they had come into possession of the highest medical degrees of certain famous British universities)

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who were "convinced" that in tuberculin they had a remedy which, when "properly" applied, was well-nigh infallible—that is, they were about as "convinced" as the authors of the Second Loveday Report on Veterinary Education (bless their little souls!) were, in their memorable conclusion, that more and better veterinarians for, among other things, the great national enterprise under review that lies ahead of us will be obtained when the graduates will have received a training similar to that of the above medical gentlemen, against whom it was useless to argue, even though ever since the time of Virchow (1891) onwards all genuine scientific observation has depicted that tuberculin applied in that way as a remedial agent may often have disastrous consequences.

There has been an endeavour on the part of medical workers, including even Bulloch, who could not contemplate dethronement of a hero, to palliate Koch, for not only yielding in the above unsavoury episode, but also for his later misleading pronouncement—as it was, to any who trouble to read his address—from false argument to infer that no steps were really called for in the public health interest to eradicate bovine tuberculosis.

We can never sufficiently pay homage to the memory of McFadyean for shattering at once that misconception. The conclusions of the Royal Commission on Tuberculosis (1901 to 1911), to which McFadyean was appointed, as well as of the similar simultaneous German Commission, and all subsequent testimony, place us in no doubt whatever now as to the nature and gravity of the dangers of infection with tuberculosis of bovine origin to man. Nevertheless, with growing enlightenment of medical workers, as well as of the public, upon the relationship and the consequent abandonment of controversial positions, it is becoming increasingly clear that each profession has a great deal to learn from interest in the work of the other.

Hardly less than with tuberculosis, the literature upon, for example, malaria has been "voluminous." It would be no great exaggeration to say in connection with it, however, that until the recent discovery of the exo-erythrocytic stages of the causal parasite in the humble fowl and the consequential all-importance of the remote tissue changes in the disease, all that had been recorded since the great discovery of the mode of transmission of the infection by Ross, in the sparrow, in 1898 ("exo-erythrocytic"), and the confirmation of that finding by Grassi for the human subject, was little more than the filling of "trivial lacunæ." Since then, with the biologist and chemist working in concert, discoveries upon means of prevention as well as cure have been phenomenal.

Contrariwise, the veterinarian may have a great deal to learn about the significance of hereditary predisposition from medical workers. Francis has touched upon this point very well in his book, and the information could, with advantage, have been much expanded. Already there is becoming available abundant evidence that cattle exhibit considerable differences in natural susceptibility. This is not only becoming portrayed in the higher degree of resistance possessed by zebu cattle. Veterinarians with much experience in the field have often been struck by the freedom from infection that continues to be displayed by odd cows maintained in an environment in which up to even ninety per cent. of the cattle are

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reactors, and in which environment therefore the infection may be presumed to be ubiquitous. The relatively low incidence of the infection among cattle in some areas, such as in some parts of Wales, also provides food for reflection. Whether much of our improved stock is thus derived from progenitors specially highly susceptible to tuberculosis is therefore a fascinating question and perhaps a not unimportant one. Its fascination, however, must not be allowed to outweigh the practical objective now that we believe that we have a clear perception of that objective: which is that, whatever are the variations in natural susceptibility or resistance of our present-day stock as we find it, there is no wise alternative to the total and complete eradication of tuberculosis using the methods the principles underlying which have long been familiar to us.

As evidence that McFadyean, even though he may not have altogether succeeded in transmitting his own talents to his immediate descendants (in the intellectual sense), may well prove to be potent at a further remove, we will quote, in preference to what has been printed in ordinary type in the main text or in bold type in the summaries, a passage from Francis's book that is printed in small type as footnote (p.26):—

"An Attested Herd is an officially tubercle-free herd under the Attested Herds Scheme introduced by the Ministry of Agriculture in 1935. Where the herd has been recognised as free from tuberculosis various rules designed to prevent the introduction of infection have to be observed. The rules provide for the prevention of infection arising from contact with cattle on neighbouring farms directly or indirectly, or arising from contact with swine or any other source of infection on the farm. They deal with shows and sales at which animals from attested herds may be included, and they control the movement of cattle on to and off the premises. A 'tuberculin tested' herd is one licensed to sell milk from tubercle-free cattle under the Milk (Special Designations) Order of 1923. The only provision is that cattle shall be tested periodically and the reactors disposed of, and like other 'public health' legislation relating to milk, it has done little to progressively increase the number of tubercle-free cattle."

Until the introduction of the Attested Herds Scheme of 1935, however, it was well appreciated that the successive schemes introduced were meant to, and almost certainly did, safeguard the "public health" interest, and that only; for, from their partial nature, they could hardly be expected to serve the agricultural interest by a real progressive decrease in the incidence of bovine tuberculosis.

We may here quote what McFadyean said as far back as 1913 in the inaugural address already mentioned (*Vet. Rec.*, 1913-14, *26*, 223), dealing with the Tuberculosis Order just then introduced as a first instalment of legislation:—

". . . . The present year (1913) has witnessed the opening of the campaign against one of the most redoubtable of animal plagues in the issue by the Board of Agriculture of the Tuberculosis Order, which came into force on May 1st last. It is curious, and to some extent discouraging, to reflect that for many years the necessity of State intervention with regard to tuberculosis in cattle has been preached by members of the veterinary profession in this country. In reality, nearly all the facts which can be adduced to justify intervention now have been

known for at least a dozen years, and most of them for nearly twice that period. They were, however, accepted by only a small number of people and they were scarcely known at all by the general public. The interval has been spent in educating the people with regard to the disease, which in this country is an indispensable preliminary to legislation. . . .

"The proceedings which have been begun under the Tuberculosis Order are therefore thoroughly rational and justifiable in so far as they aim at the prevention of human infection with tubercle bacilli derived from cattle.

"The new Order will bring a large amount of new work to the veterinary profession, and it would be affectation to deny that it is welcome on that account. It is to be hoped that members of the profession will be equally impressed with the fact that the Order charges them with a very great responsibility, as its success will largely depend upon their knowledge and their skill in the matter of diagnosis. It is obvious, however, that the primary responsibility for the successful working of the Order will fall upon the Local Authorities and the owners of cattle, and most of all on the latter, as without honest notification of suspected cases little benefit can be expected from the Order.

"The new Order is not an attempt to stamp out bovine tuberculosis, or at any rate it is not calculated to bring about that result. *It is not even the opening of the battle against the disease, but a mere reconnaissance to explore the position of the enemy. This, in my opinion, is not a defect, but a merit of the Order. The compulsory testing of all cattle in the country, to be followed by the slaughter of all reacting animals, is a plan which no sane and well-informed person could recommend. The only wise plan appears to be to attack the disease gradually, and to extend and strengthen the procedures adopted in accordance with the experience gained. . . .*" (our italics).

Until 1935, therefore, the real battle with the enemy had not been joined. The years of world war have caused dislocation in the attack. But, all in all, the prospects of real victory are rapidly brightening.

It is a commonplace recommendation of a reviewer after commenting upon a book that has gained his favour to say that it should find a place on the shelves of every veterinary surgeon. Francis's book is not one that should be shelved. It should be bought by every veterinary surgeon and kept near his person till it is thoroughly assimilated. Then, when that is done, it is to be hoped that the veterinary surgeon will strive by his own efforts to add materially to the facts reported in it and so help to bring forth another edition soon that will record a resounding triumph for the British veterinary profession.

REVIEWS

The UFAW Handbook on the Care and Management of Laboratory Animals. Edited by A. N. Worden (Milford Professor in Animal Health, University College of Wales, Aberystwyth), 1947. London: Baillière, Tindall & Cox. Pp. xvi + 368; 70 illustrations. Price: 31s. 6d.

This handbook, which owes its production to the Universities Federation for Animal Welfare (UFAW), is intended to serve as a guide and reference text to

practices in the housing, feeding and management of the commoner animals used in connection with laboratory procedures. Each of the several chapters dealing with a specific animal is the work of someone having detailed knowledge and experience of the type, whilst the editing of the separate contributions and their compilation for publication in book form has been carried out by Professor Alastair Worden, who is also responsible for numerous text additions and several lists of extra references.

Species, in addition to the usual four of laboratory rodents, which receive more or less complete consideration comprise the black rat, wild house-mouse, deer mouse, cotton rat, common (field) vole, Orkney vole, golden hamster, ferret and hedgehog. Bird subjects are represented by the pigeon and the canary, whilst various commonly-kept amphibians and also *Xenopus lævis* receive attention, the latter in some detail. A chapter on freshwater fish gives useful information about the keeping of the several species preferred for use in physiological investigations, as test animals in the study of water pollution, and for the assay of certain medicinal substances. A series of notes giving references to sources of information is provided for certain species having only specialised laboratory uses—monkeys and apes, dogs and cats, horses and other ungulates, shrews, vampire bats, poultry, reptiles and few invertebrates.

The subject matter in each of the chapters given over to one particular species is itemised and clearly sub-titled according to a uniform plan—introduction; accommodation; nutrition; breeding; handling and marking; anæsthesia and euthanasia; and disease and its control.

Separate chapters are also included on "Law and Practice" in relation to laboratory animals; "The Animal Laboratory," giving details about the construction and layout of houses, together with examples of cages and other equipment which have proved suitable in particular laboratories; and "Pests of the Animal House and their Control." A lengthy appendix of some seventy pages having the impressive heading, "A Conspectus of the Elements of Statistical Analysis," seems to the reviewer to be somewhat out of place in a book of this kind, all the more so since there are available several excellent and well-known monographs on this subject.

The quality of the individual contributions is variable, as is to be expected, but in so far as each reflects the first-hand experience of its writer they constitute valuable accretions to the written information on the subject of laboratory animal maintenance. Professor Dalling in his Foreword aptly implies a function which the handbook will undoubtedly perform in no small measure, viz., that it will make more generally available that kind of information which has hitherto "been largely confined to the place in which the knowledge was gained, and only exceptionally has it been available to other laboratories."

Viewed as a whole, this handbook provides a valuable compendium of essential information on the breeding and management of small laboratory species, and should, therefore, be placed in the hands of every tyro entering experimental research, and also similarly be made available to the animal attendant who will yet learn much from its constant study. To the research worker of longer standing,

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the extensive bibliographies and reference lists should prove a specially acceptable feature. Lastly, but by no means least, the general veterinary practitioner will find within this book a not inconsiderable body of information which will on many occasions be of direct application to his immediate preoccupation and work.

N.J.S.

Manual of Comparative Anatomy. By OSMOND P. BRELAND, Ph.D., University of Texas. McGraw-Hill Publishing Company. Price: 15s.

THE author's intention is to enable the student to identify the structures under discussion almost without the help of demonstrators. The directions are planned well and clearly set out. It is unfortunate that the book is devoid of illustrations for they often express things more clearly than words.

The author's second purpose is to emphasise the comparative significance of structures rather than a knowledge of structure for its own sake. Thus, valuable paragraphs are inserted at intervals to correlate the various systems found in different forms. Some systems, however, are neglected in this respect, notably the nervous system. Type animals described are amphioxus, the lamprey, the dogfish, the perch, necturus, the turtle, and the cat. The dogfish and cat receive the most attention. Except for the cat, the general level is moderately elementary. One or two factual statements might draw comment. For example, the origin of biceps brachii is given (page 190) as glenoid fossa; admittedly, the origin in the cat is unusually near the edge of the glenoid fossa, but clearly no tendon could arise from the actual articular cavity. However, this inexactitude is repeated elsewhere. Again, the veterinary or human anatomist would notice with disapproval that there is still no differentiation between pleural and thoracic cavity, etc., so that the pleural cavity is described as containing the lung. And lastly, there is the the observation (page 206) that the vas deferens enters the bladder—an arrangement with obvious functional disadvantages. The general standard of production of the book is good average: the paper is not good, but the binding is strong, the cover very durable and well turned out.

A.S.K.

Animal Ecology. By A. S. PEARSE, Professor of Zoology, Duke University. Published by McGraw-Hill Book Co., Ltd. Price: 35s.

THIS book should be of interest to any person with a small knowledge of biology and a developing interest in animals and their relationship to environment. The author deals with the subject in a general manner, the result being a very readable book which encompasses a wide field but does not discuss every aspect in great detail. The first part of the book is concerned largely with ecological factors

in general, for example, light, temperature, nutrition, etc.; this is followed by a chapter on rhythms or the periodic fluctuations in the stability of animals and the factors that influence those rhythms. The author then proceeds to consider the ocean, freshwater and the land as habitats and explains the various phenomena which may be encountered in each environment. He goes on to discuss the inter and intra specific relations of animals and concludes with short chapters on economic ecology and the teaching and problems of ecology. The book as a whole is well turned out, especially considering the handicaps imposed on the publishers by present-day restrictions. The binding is good and the paper of average texture. The photographs, unfortunately, leave a lot to be desired, some being very poor indeed. However, a wide field of study is dealt with very competently and a lot of profitable reading should be found within these pages.

D.Z.K.

CHIEF VETERINARY OFFICER OF THE MINISTRY OF AGRICULTURE AND FISHERIES

It has recently been announced that Mr. T. Dalling, M.A., M.R.C.V.S., F.R.S.E., is to succeed Sir Daniel Cabot, M.R.C.V.S., as Chief Veterinary Officer of the Ministry of Agriculture and Fisheries.

Mr. Dalling is the director of the Veterinary Laboratory of the Ministry at Weybridge, a post which he has held since 1942. His previous posts were: Professor of Animal Pathology, University of Cambridge; Veterinary Superintendent, Wellcome Physiological Research Laboratories; and Chief Investigator, Animal Diseases Research Association, Scotland.

Sir Daniel Cabot, who retires on August 21, joined the Ministry in 1911 and attained the post of Chief Veterinary Officer in 1938. His services are being retained part-time in a temporary capacity in connection with certain international veterinary organisations.

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